Remarks

Claims 1-33 are pending. Claims 14-20 and 29-33 have been withdrawn. Claim 10 is canceled herein. Therefore, claims 1-9, 11-13, and 21-28 are under consideration.

35 U.S.C. 112, first paragraph

Claim 10 has been rejected under 35 U.S.C. 112, first paragraph, for allegedly lacking enablement. In particular, the Examiner has rejected claim 10 for listing UCHT1-CRM9 immunotoxin which is allegedly not "known and readily available to the public or obtainable by a repeatable method as set forth in the specification." Applicants maintain their position regarding the availability of UCHT1-CRM9 for reasons of record. However, in an effort to further prosecution, Applicants cancel claim 10 herein. Therefore, this rejection is now moot. Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. 112, second paragraph

Claim 10 has been rejected under 35 U.S.C. 112, second paragraph, for allegedly being indefinite. In particular, the Examiner has rejected claim 10 because allegedly the "recitation 'UCHT1-CRM9' is merely a laboratory designation which does not clearly define the claimed product." Applicants maintain their position regarding the indefiniteness of "UCHT1-CRM9" for reasons of record. However, in an effort to further prosecution, Applicants cancel claim 10 herein. Therefore, this rejection is now moot. Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. 103(a)

Claims 1-13 and 21-28 are rejected under 35 USC 103(a) as allegedly being obvious over Neville et al. (U.S. Patent No. 6,103,235) in view of Sykes et al. (U.S. Patent No. 6,514,513) and/or Gray et al. (U.S. Patent No. 6,754,334) and in further view of Strom et al. (in Therapeutic Immunology, edited by Austen et al., Blackwell Science, Cambridge MA, 1996 p451-6). Specifically, the Office Action alleges that Neville et al. teaches "methods of inducing immune tolerance or immunological non-responsiveness to foreign mammalian donor organs or cells...by safely exposing the recipient so as to reduce the recipient T cells with anti-CD3 immunotoxins." The Office Action acknowledges that Neville et al. does not teach co-stimulatory blockers or their use to promote graft survival.

The Office Action goes on to allege that Sykes et al. teaches "methods of inducing tolerance to foreign antigens...by administering a co-stimulatory blocker, including CTLAIg including combination with T cell depletion or inactivation with anti-T cell antibodies." The Office Action concedes that Sykes et al. does not teach anti-CD3 immunotoxins.

The Office Action also alleges that Gray et al. teach the "use of CTLA-4 Ig fusion proteins for down regulating immune responses inducing non-responsiveness...in combination with agents that inhibit T cells or induce general immunosupression. As with Sykes et al., the Office Action acknowledges, that Gray et al. does not teach the anti-CD3 immunotoxins used in the present claims.

Lastly, the Office Action alleges that Strom et al. teaches "a multi-tiered approach to immunosuppressive therapy." The Office Action also alleges that Strom et al. teaches the future use of "antibodies and fusion proteins that target discrete steps in antigen recognition, signal transduction, and effector immunity."

Applicants respectfully traverse the rejection. The present claims recite a method with the following elements:

1) "chronic" transplant rejection

2) anti-CD3 immunotoxin and

3) costimulation blocker.

In order to establish a prima facie case of obviousness, the Examiner must satisfy three criteria. First, all the limitations of the claim must be taught. Second, there must be some suggestion or motivation to modify or combine the references either in the references themselves or in the general knowledge of one of skill in the art. Lastly, there must be a reasonable expectation of success. Applicants respectfully submit that at least the last two criteria have not been met.

With respect to the motivation to combine the references, it is well established that simply "because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references." *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). Here, the Examiner has not shown why one of skill in the art would want to make the particular claimed combination. The Examiner's sole

stated motivation to combine references rests on the belief that "different targets and mechanisms of action... increase immunosuppression while decreasing the undesirable effects of immunosuppression therapy." Thus, allegedly, one of skill in the art would be motivated to combine any known method for inhibiting chronic transplant rejection with any other method for inhibiting chronic transplant rejection for the alleged purpose of deriving allegedly known advantages from combination therapy. However, no teaching in the references themselves or in the general knowledge in the art suggests making the particular combination claimed in the present application. Strom et al. discloses that a multi-tiered approach may be successful, but does not provide guidance as to which combination should be tried and, in particular, does not suggest the combination of an anti-CD3 immunotoxin and co-stimulation blockade. Neville et al., describes only the use of the anti-CD3 immunotoxin with general immunosuppressive agents such as cyclosporine, but notably does not even mention chronic transplant rejection. Sykes et al., describes co-stimulation blockade for immunotherapy, but only mentions multi-tiered treatments involving multiple co-stimulatory blockers (column 38, lines 20-44) or "agents which inhibit the production, levels, or activity of antibodies in the recipient" (column 39, lines 35-40). Likewise, Gray et al. only describes a "multi-tiered" approach with respect to multiple co-stimulation blockers (column 22, lines 38-42). Thus, even if Strom et al. is deemed sufficient to provide general motivation to combine the references, Neville et al., Sykes et al., and Gray et al., fail to provide the specific motivation to arrive at the specifically claimed method. This situation is illustrative of the principle that, "the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir.1990). Nowhere in the cited references is the above combination of elements implicated, hinted at or explicitly suggested. Therefore, none of the references alone or in combination provide motivation for the particular combination claimed. Moreover, the failure of all of Strom et al., Sykes et al., or Gray et al., to suggest a combination or multi-tiered approach that includes immunotoxins indicates that the claimed combination therapy was outside the mainstream of the art and thus not obvious.

Thus, the cited publications do not, either alone or in any combination, provide a suggestion or sufficient motivation to even try combine anti-CD3-immunotoxin therapy with co-

stimulatory blockade. As nowhere in the prior art is the desirability of the combination suggested, the only reason for combining the various teachings of the references is the subjective goal of making Applicants' invention appear obvious, and any such interpretation can only be based on improper hindsight based on the Examiner's knowledge of the Applicant's current invention.

Moreover, as noted above, the cited publications do not disclose or suggest the claimed combination of anti-CD3-immunotoxin therapy with co-stimulatory blockade. The Office Action merely asserts that it would have been obvious to make the claimed combination and provides as motivation only an assumed desire by those of skill in the art to improve upon patented solutions to the problem of transplant rejection (Sykes et al. and Gray et al.) by combining those solutions with a method (Neville et al.) that does not disclose let alone teach chronic transplant rejection to arrive at the presently claimed invention. No evidence is presented to support these conclusions. By the apparent logic of the rejection, any combination of treatment methods would be obvious as long as some speculative reason for combination could be articulated in hindsight. With respect to motivation or suggestion to combine the references, the Examiner asserts that Strom et al. provides the motivation for this combination. Specifically, the Examiner states that "Strom notes the known multi-tiered approach to immunosuppressive therapy in that several agents are used simultaneously." Applicants note that Strom et al. suggests a different multi-tiered approach, and does not suggest or discuss the particular combination claimed herein. Moreover, the remaining references of Neville et al., Sykes et al., and Gray et al. do not suggest or discuss the particular combination claimed herein and Neville et al. does not even suggest that its method might be relevant to chronic transplant rejection. Thus, alone or in combination the references fail to suggest the particular combination claimed. For at least these reasons, the Examiner has failed to establish motivation to combine the references and thus failed to establish a claim of obviousness. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

In addition to not providing any motivation to combine the teachings, none of Neville et al., Sykes et al., Gray et al., or Strom et al. provide any guidance as to which combinations would be necessary to prevent chronic transplant rejection or reap the benefits of combination therapy touted as motivation for such combinations. Strom only teaches the use of a multi-tiered

approach, but does not provide guidance as to which combination should be tried and, in particular, does not suggest the combination of an anti-CD3 immunotoxin and co-stimulation blockade for inhibiting chronic transplant rejection as claimed herein. In fact, Strom et al. merely states that broad categories of improvements are anticipated such as "new drugs, [and] humanized mAbs [monoclonal antibodies]." Strom et al. p455. Following the logic of the Office Action, Strom et al. would also be cited for rendering any new humanized mAbs or new drugs obvious. Thus, at best, Strom et al. can be used as evidence that it would be obvious to try various immunosuppressive therapies to find a combination that provides improved results. At best, the remaining references provide disconnected examples of immunosuppressive therapies. However, as noted in *In re O'Farrell* 853 F.2d 894 (Fed. Cir. 1988), "obvious to try" is an improper standard under 35 USC 103 for showing a reasonable likelihood of success. This situation is analogous to the situation described by the court in *In re O'Farrell*. Specifically the court stated that:

> In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.... In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *Id* at 903.

In addition, it is well known in the case law that a proper analysis of a rejection under 35 U.S.C. § 103 requires not only evidence and reasoned arguments that the cited art provides motivation to produce the claimed invention, but also evidence and reasoned arguments that, based solely on the teachings of the cited art, one of ordinary skill in the art would have a reasonable expectation of success in producing the claimed invention. See *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). ("Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed [invention]; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success."); *In re Dow Chemical Co.*, 837

F.2d 469, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988) ("The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art...Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure").

The method claimed herein is directed to chronic transplant rejection. "Chronic rejection is not simply delayed acute rejection. Rather it represents a pathological tissue remodeling response that develops at a variable rate as a consequence of peritransplant and posttransplant vascular trauma." (Van Buskirk et al., (1997) JAMA 278:1993-1999, included herein as exhibit A). Notably, Van Buskirk et al. indicate that there is "no accepted therapeutic strategy" for the treatment of chronic rejection using convention immunosuppressant regimens. *Id.* at 1998. Thus, at the time the present application was filed, none of the cited art was deemed successful at treating chronic transplant rejection. In fact, Strom et al. is further evidence that even with a multi-tiered approach, prior to the presently claimed methods, protocols for treating chronic transplant rejection were not successful. Strom et al. states "Although current drug protocols are far superior to those used a decade ago, the situation is far from ideal. Most allografts eventually succumb to chronic rejection (emphasis added)." Strom et al. p455. Notably the multi-tiered approach is presented in Strom et al. not as a future modification to protocol in use, but as an existing protocol. Moreover, because Gray et al., Sykes et al., and Strom et al. alone or in combination were not successful at treating chronic transplant rejection, according to the teachings of Van Buskirk and Strom, there would not be a reasonable expectation of success for one of skill in the art to successfully inhibit chronic transplant rejection by combining those teachings with a method that discloses an anti-CD3 immunotoxin but does not suggest its use in chronic transplant rejection. Such a suggestion is the equivalent to saying that by combining methods known not to work in a particular situation with a method untested for the situation, one of skill in the art would reasonably expect the new combined method to work for the same situation. In fact, such arguments more reasonably suggest that any success would be surprising and unexpected as is the case for treating chronic transplant rejection as taught herein. Therefore, neither the references nor the general knowledge in the art would provide one of skill in the art a reasonable expectation of success in practicing the methods claimed herein. For at

least these reasons, the Examiner has failed to establish a reasonable expectation of success and thus failed to establish a claim of obviousness.

Having failed to establish an objective basis to combine the cited references and failed to recite how the references provide a reasonable expectation of success, a prima facie case of obviousness is not presented. Applicants believe this rejection to be overcome and respectfully request its withdrawal.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $620.00, representing $500.00 the fee for a Notice of Appeal under 37 C.F.R. § 41.20(b)(1) and $120.00 for a one (1) month extension of time fee for a large entity under 37 C.F.R. § 1.17(a)(1) and a Request for Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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J. Gibson Lanier — Date: 1/17/06